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CANCER RISK FOLLOWING PRIMARY HEMOCHROMATOSIS: A POPULATION-BASED COHORT STUDY IN DENMARK

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A population-based cohort of 120 Danish men, discharged with a hospital diagnosis of primary hemochromatosis from 1977 to 1989, was followed up to 1989 for subsequent cancer risk. Nineteen subjects (including 6 with primary liver cancers) were excluded from the analysis, either because they died within the same month of hemochromatosis diagnosis or because they had cancer prior to diagnosis of hemochromatosis. Among the 101 remaining subjects, 4 primary liver cancers occurred one year or more after the diagnosis of hemochromatosis, far surpassing the expected number based on incidence rates from the Danish population (standardized incidence ratio 92.9, 95% confidence interval 25.0 to 237.9). The excess of liver cancer was associated with cirrhosis and included cholangiocarcinoma as well as hepatocellular carcinoma. Significantly elevated risks were also observed for non-hepatic cancers (13 cases; SIR 3.5, 95% CI 1.9 to 6.0), notably esophageal cancer (2 cases; SIR 42.9, 95% CI 4.8 to 154.9) and skin melanoma (2 cases; SIR 27.8, 95% CI 3.1 to 100.3). The results of this population-based study are in accordance with the hypothesis that patients with primary hemochromatosis have a substantial risk of primary liver cancer. Further studies of hemochromatosis may be useful in clarifying the relation of non-hepatic malignancies to body iron stores in the general population.

Primary hemochromatosis is a genetic disorder with an autosomal recessive mode of inheritance (Bradbear *et al.,* 1992). It is characterized by excessive absorption and accumulation of iron in most organs, especially in hepatocytes, leading to hepatic cirrhosis, diabetes mellitus, arthritis, cardiomyopathy and hypogonadism (Bradbear *et al.,* 1992). The clinically apparent disease is more common in men, who generally consume more food and thus absorb more iron, while women tend to lose iron intermittently during menstruation and pregnancy. In addition to autopsy and clinical reports, 2 follow-up studies have shown that the risk of primary liver cancer (PLC), especially hepatocellular carcinoma (HCC), is very high among patients with hemochromatosis complicated by liver cirrhosis (Niederau *et al.,* 1985; Bradbear *et al.,* 1985). Earlier surveys of hemochromatosis patients indicated that about 7% developed PLC, although more recently the proportion has risen to almost 30% (Bradbear *et al.,* 1992). This increase probably reflects longer survival of hemochromatosis patients due to earlier detection and more effective therapy by periodic venesections.

Although the evidence is not conclusive, some clinical reports have suggested that non-cirrhotic patients with hemochromatosis may have an increased risk of PLC (Blumberg *et al.,* 1988; Deugnier *et al.,* 1993), while other studies have suggested that hemochromatosis may predispose to non-hepatic cancers (Ammann *et al.,* 1980; Deugnier *et al.,* 1993). Thus, hemochromatosis may be a useful model for clarifying recent epidemiologic concerns about the possible relation of various tumors to body iron stores (Knekt *et al.,* 1994). To investigate further the risk of PLC and other cancers associated with primary hemochromatosis, we carried out a population-based cohort study to estimate cancer risk among 120 male patients hospitalized with primary hemochromatosis from 1977 to 1989 in Denmark.

SUBJECTS AND METHODS

Since 1977, the Danish Central Hospital Discharge Register (DHDR) has recorded all hospital discharges in Denmark. Each record contains data on identification number, residence, hospital department, surgical procedures, and up to 20 discharge diagnoses (Danish Cancer Registry, 1989). These diagnoses were coded according to the 8th revision of the International Classification of Diseases (ICD). Approximately 1 million discharges are recorded annually for the 5 million inhabitants of Denmark.

To assemble the cohort, all men whose records in the DHDR contained a diagnostic code for primary hemochromatosis (Danish ICD8 273.29) between 1977 and 1989 were included. A complete history of discharge diagnoses since 1977 was obtained for all cohort members.

Information on cancer occurrence among cohort members was obtained by use of record linkage with the Danish Cancer Registry (DCR) with follow-up through 1989. Each Danish citizen has a unique 10-digit personal identification number that allows such linkage, and by law all cancer cases must be reported to the DCR at time of diagnosis. To produce an accurate estimate of person-years of follow-up, linkage was made to the Danish Central Population Register, which contains vital and migration information on all Danish residents since 1968. Study subjects were followed from the date of the first hospital discharge for hemochromatosis until the date of cancer diagnosis, date of death, or December 31, 1989, whichever occurred first.

The expected number of cases was calculated by multiplying the number of person-years by the age-specific cancer-incidence rates in Denmark for each five-year age-group and calendar-period of observation. Since the general population is large and the cancer incidence is small, the observed cancers can be assumed to follow a Poisson distribution, with a mean value equal to the expected number derived from the population. The standardized incidence ratio (SIR), the ratio of observed-to-expected cancer cases, and its 95% confidence interval (CI) were computed to quantify the associations between primary hemochromatosis and cancer (Bailar and Ederer, 1964).

RESULTS

Between 1977 and 1989, 120 male subjects with hemochromatosis were registered in the DHDR. Nineteen subjects were

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TABLE I – STANDARDIZED INCIDENCE RATIO (SIR)[1] OF PRIMARY LIVER CANCER AMONG MALE HEMOCHROMATOSIS PATIENTS (DENMARK, 1977–1989)

	Observed	SIR	95% CI
Years since first admission for hemochromatosis			
<1	3	338.8	68.1–989.8
1–2	1	162.8	2.1–905.6
3–5	0	—	—
6–13	3	223.3	44.9–652.5
Years 1–13[2]	4	92.9	25.0–237.9
Age at diagnosis of hemochromatosis			
<60	1	51.6	0.7–287.0
60–69	2	142.9	16.1–516.0
70–80	1	103.4	1.4–575.6
Year of diagnosis of hemochromatosis			
1977–1979	1	67.6	0.9–376.0
1980–1984	2	84.2	9.5–304.1
1985–1989	1	222.1	2.9–1235.5

[1]Adjusted for age.–[2]Excluded 3 primary-liver-cancer patients diagnosed within the first 12 months of hemochromatosis diagnosis.

excluded from the analysis, either because they died in the same month as the hemochromatosis diagnosis (n = 14) or because they were reported with cancer before hemochromatosis (n = 5). Among the excluded 19 subjects, 6 had PLC (4 HCC, 1 cholangiocarcinoma and 1 unclassified). The remaining 101 men in the analysis accrued 401 person-years and developed 20 cancers (SIR 5.4, 95% CI 3.3 to 8.3), including 7 PLCs (3 detected between 1 and 12 months after diagnosis of hemochromatosis and 4 occurring one year or more later). Of the 7 PLCs, 4 were HCC, 2 were cholangiocarcinoma, and 1 was unclassified; 6 of the 7 PLC cases had liver cirrhosis noted in the available records.

In the cohort of 101 men, 20 (19%) patients had liver cirrhosis, 42 (40%) diabetes, and 2 (2%) hepatitis. None of the PLC patients had hepatitis or alcoholism mentioned in the discharge records, but they all had diabetes. Since 43 (41%) subjects died during the study period, the average follow-up was relatively short (4.1 years). The mean age at diagnosis was 54.6 (range 25 to 80) for hemochromatosis and 62.5 (range 55 to 71) for PLC.

As shown in Table I, the excess risk of PLC one year or more after diagnosis of hemochromatosis was 93-fold (SIR 92.9, 95% CI 25.0 to 237.9). Although based on small numbers, the risk persisted across time intervals, age groups, and calendar periods. In addition, significantly elevated risks were seen for non-hepatic cancer (13 cases; SIR 3.5, 95% CI 1.9 to 6.0), especially cancer of the esophagus (2 cases; SIR 42.9, 95% CI 4.8 to 154.9), and melanoma of the skin (2 cases; SIR 27.8, 95% CI 3.1 to 100.3). There was one case of extra-hepatic bile-duct cancer *vs.* 0.02 expected. Three cases of lung cancer (SIR 4.0, 95% CI 0.8 to 11.5) and one of pleural cancer (mesothelioma) (SIR 56.0, 95% CI 0.7 to 311.8) were also observed.

DISCUSSION

The 93-fold risk of PLC in our cohort study, based on 4 cases that occurred at least one year after the diagnosis of primary hemochromatosis, is slightly lower than the 125-fold risk reported in other follow-up studies (Bradbear *et al.,* 1985; Niederau *et al.,* 1985). Our risk estimate utilized the most conservative approach by including only the 4 incident cases, while excluding 9 PLCs detected before the diagnosis of hemochromatosis (6 cases) or from 1 to 12 months after the diagnosis (3 cases). Thus, among the initial 120 men with hemochromatosis, 11% (13 cases) had PLC, which is less than the 30% reported in some earlier clinical series (Bradbear *et al.,* 1992), and which may reflect the relatively short follow-up period of our study.

The pathogenesis of PLC in primary hemochromatosis is unclear, but it probably involves the cirrhotic process that was documented in 6 patients in our series and in the literature. However, the exceptionally high risk of PLC suggests that hepatic iron deposits may exert additional effects, such as promoting tumor growth, inhibiting the tumor-killing properties of macrophages (Stevens, 1992) and facilitating the persistence of hepatitis-B or -C infection (Stevens *et al.,* 1983). While most liver tumors seen with hemochromatosis have been hepatocellular carcinomas, the excess risk appears to extend to cholangiocarcinoma (intra-hepatic bile-duct cancer) (Niederau *et al.,* 1985) as seen during follow-up of 2 patients in our series, and perhaps to hepatic angiosarcoma, based on rare case reports (Sussman *et al.,* 1974). In view of the risk of cholangiocarcinoma in hemochromatosis, it is noteworthy that another patient in our survey had extra-hepatic bile-duct cancer.

Some surveys have suggested an excess of non-hepatic cancers among patients with hemochromatosis (Ammann *et al.,* 1980; Deugnier *et al.,* 1993) and among healthy subjects with elevated body stores of iron (Knekt *et al.,* 1994; Stevens, 1992; Stevens *et al.,* 1994), but the epidemiologic evidence on both counts is inconclusive. Although our survey was based on small numbers, we found some evidence for an elevated risk of non-hepatic cancer, with significant excesses of esophageal cancer and skin melanoma, and with non-significant increases of lung cancer and pleural mesothelioma. This study did not find the excess of colon cancer recently reported among persons with high stores of body iron (Knekt *et al.,* 1994). Further studies are needed to clarify the risk of non-hepatic cancer among hemochromatosis patients and others in the general population with high iron stores.

Several limitations of this study should be noted. First, only patients with primary hemochromatosis whose symptoms warranted hospitalization were included in the study. Although hemochromatosis is generally considered a rare disorder, the gene frequency of this disease is estimated to be 3 to 8% in Caucasians, and the homozygote frequency about 0.25 to 0.5% (Edwards *et al.,* 1988). Second, the sample size was small and the follow-up period was short (average 4.1 years), although some patients were traced up to 13 years. Third, we had little information on other determinants of PLC, such as alcohol intake, smoking, and hepatitis-B/C infections. However, none of the subjects in the cohort had alcoholism mentioned in his discharge record, and only 2 had had hepatitis. The strong association between hemochromatosis and PLC (SIR 93) is unlikely to be explained by the confounding effects of alcohol or other causal factors for liver cancer. In a Swedish study, the relative risks of PLC associated with alcoholism, liver cirrhosis without alcoholism, and alcoholic cirrhosis were 3.1, 35.1, and 34.3 respectively (Adami *et al.,* 1992), far smaller than the risk observed with hemochromatosis. Finally, misclassification of primary hemochromatosis is possible in some cases, since the inclusion of patients was based on the information available from hospital discharge records.

In summary, this population-based cohort study is in accordance with the hypothesis that patients with hemochromatosis complicated by liver cirrhosis have a marked excess risk of PLC. Although our study suggests that other malignancies may occur excessively in hemochromatosis, the findings are based on small numbers, and further research is needed.

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